



BILLING CODE 4163-18-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Centers for Disease Control and Prevention

**National Health and Nutrition Examination Survey (NHANES)
DNA Specimens: Guidelines for Proposals to Use Specimens
and Cost Schedule**

AGENCY: Centers for Disease Control and Prevention (CDC),
Department of Health and Human Services (HHS).

ACTION: Notice.

SUMMARY:

The Centers for Disease Control and Prevention (CDC), located within the Department of Health and Human Services (HHS) announces reopening of the National Center for Health Statistics' (NCHS) National Health and Nutrition Examination Survey (NHANES) DNA Specimen Repository for research proposals. Blood samples for DNA purification were collected from study participants during NHANES III, NHANES 1999-2000, NHANES 2001-02, NHANES 2007-08, and NHANES 2009-

10 (Office of Management and Budget Control Numbers 0920-0237/0920-0950). Samples from these DNA Specimens are being made available to the research community for genetic testing. The information gained from research using these samples can be combined with the extensive amount of information available in NHANES which describes the prevalence/trends of disease, nutrition, risk behaviors, and environmental exposures in the US population. A more complete description of this program follows.

FOR FURTHER INFORMATION CONTACT NHANES GENETIC PROJECT

OFFICER: Jody McLean M.P.H., Division of Health and Nutrition Examination Surveys, National Center for Health Statistics, Centers for Disease Control and Prevention, 3311 Toledo Road, Hyattsville, MD 20782, Phone: 301-458-4683, Fax: 301-458-4029, E-Mail: NHANESgenetics@cdc.gov.

Authority: Sections 301, 306 and 308 of the Public Health Service Act (42 U.S.C. 241, 2421 and 242m).

SUPPLEMENTARY INFORMATION

Background

NHANES is a program of periodic surveys conducted by NCHS. Examination surveys conducted since 1960 by NCHS have provided national estimates of the health and nutritional status of the U.S. civilian non-institutionalized population. The goals of NHANES are (1) to estimate the number and percentage of people in the U.S. population and designated subgroups with selected diseases and risk factors for those diseases; (2) to monitor trends in the prevalence, awareness, treatment and control of selected diseases; (3) to monitor trends in risk behaviors and environmental exposures; (4) to analyze risk factors for selected diseases; (5) to study the relation among diet, nutrition and health; (6) to explore emerging public health issues and new technologies; and (7) to establish and maintain a national probability sample of baseline information on health and nutritional status.

The availability of the NHANES III DNA specimens has been previously announced in 2002 (67 FR 51585), 2006 (71 FR 22248), 2007 (72 FR 59094), 2009 (74 FR 45644), and 2010 (75 FR 32191). NHANES III Phase II DNA specimens (1991-1994) are from participants ages 12 or older (see NHANES III DNA Specimens section for a description). For details about available NHANES III non-genetic data see <http://www.cdc.gov/nchs/nhanes/nh3data.htm>.

Beginning in 1999, NHANES became a continuous, annual survey rather than a periodic survey. For a variety of reasons, including disclosure and reliability issues, the survey data are released as public use data files every two years. In addition to the analysis of data from any two year cycle, it is possible to combine two cycles to increase sample size and analytic options. Blood samples for DNA purification were collected from participants aged 20 years and older in survey years 1999-2002 and 2007-12. DNA specimens are available as collections from NHANES 1999-2002 (NHANES 1999-2000 and 2001-02 specimens available as one collection), and NHANES two-year cycles 2007-08 and 2009-10 (see NHANES 1999-2002, 2007-08, and 2009-10 DNA specimens section for a description). Availability of DNA specimens from NHANES 2011-12 is forthcoming and will be announced in a future FRN. The availability of the NHANES 1999-2002 and NHANES 2007-08 DNA specimens has been previously announced (Thursday, September 3, 2009 [74 FR 45644], and Monday, June 7, 2010 [75 FR 32191]). The data release cycle for the NHANES corresponding to the period in which specimens were collected for DNA is described in the following web links:

http://wwwn.cdc.gov/nchs/nhanes/search/nhanes99_00.aspx,

http://wwwn.cdc.gov/nchs/nhanes/search/nhanes01_02.aspx,

http://wwwn.cdc.gov/nchs/nhanes/search/nhanes07_08.aspx,
and http://wwwn.cdc.gov/Nchs/Nhanes/Search/nhanes09_10.aspx.

Identifiable health information collected in the NHANES is kept in strictest confidence. During the informed consent process, survey participants are assured that data collected will be used only for stated purposes and will not be disclosed or released to others without the consent of the individual in accordance with section 308(d) of the Public Health Service Act (42 U.S.C. 242m). During NHANES III, participants 12 years and older (parent or guardian signed the consent form if the participant was under age 18 years) signed a consent form to store a sample of their blood for future research. In NHANES 1999–2002, 2007–08 and 2009–10 a separate consent form was signed by eligible participants who agreed to the storing of specimens for future genetic research. DNA specimens will be available for testing only from participants who consented to future genetic research. Resulting data from DNA specimen testing will be linked to the NCHS variables (public use and restricted) and available for analyses through an NCHS Research Data Center (RDC). Access to these data at an NCHS RDC is only through an approved proposal process mechanism to assure confidentiality.

Research Proposal

Note: the following proposal types differ from those used in previous announcements for use of NHANES III DNA specimens (Thursday, August 8, 2002 [67 FR 51585], Friday, January 13, 2006 [71 FR 22248], and Monday, June 10, 2010 [75 FR 32191]).

Proposals testing a complete NHANES DNA collection of specimens (NHANES III, 7,159 samples; NHANES 1999-2002, 7,839 specimens; NHANES 2007-08, 4,612 specimens; NHANES 2009-10, 4,893 specimens):

Note: If the investigator would like to propose a subsample of the complete set please contact the NHANES Genetic Project Officer to discuss feasibility.

Proposals should investigate specific research hypotheses. The investigator will specify which DNA collection they are requesting and the tests to be conducted on DNA specimens excluding tests that produce incidental findings. The investigator will also include in the research protocol an analytic plan that includes a list of proposed NCHS variables (public use and restricted) that would be used for the data analyses. The investigator will conduct the tests of the approved variants or approved assays on

samples of NHANES DNA specimens that are labeled with a lab identification number that is not directly linkable to the public use file and therefore, anonymous to the investigator. Investigators are required to provide the data obtained from DNA testing to Division of Health and Nutrition Examination Survey (DHANES)/NCHS for quality control assessment. Analysis and linkage of the resulting data are conducted in the NCHS RDC via a separate proposal.

After the DHANES/NCHS has completed the initial quality control assessment, investigators will be given up to six months to conduct a comprehensive quality assurance review. The timeframe allowed for this review will depend on the number and characteristics of the tests submitted. At the completion of this review, the availability of the resulting data will be announced to the public on the NHANES website Genetic Variant Search:

<http://www.nhgeneticvariant.com/>. The resulting data can be linked to other NCHS variables (public use and restricted) for secondary data analysis. For further information on available variant data visit:

<http://www.cdc.gov/nchs/nhanes/biospecimens/dnaspecimens.htm#Genetic>.

DNA specimen collections will be provided in 96 well plates to investigators and distributed as samples from a complete collection or from a subsample of a collection.

Proposals testing DNA specimens already obtained from previous solicitations:

Investigators that have obtained samples from NHANES DNA specimens from previous solicitations and have sufficient DNA left may request to do additional tests on the remaining DNA. These proposals must be submitted and approved before the DNA specimens were scheduled to be destroyed or returned. The investigator will specify the test to be conducted on the samples excluding tests that produce incidental findings. The investigator will also include in the research protocol an analytic plan that includes a list of proposed NCHS variables (public use and restricted) that would be used for the data analyses.

DNA Samples

These DNA specimens (NHANES III, NHANES 1999-2002, NHANES 2007-08 and NHANES 2009-10) were processed by the Centers for Disease Control and Prevention (CDC), National

Center for Environmental Health (NCEH), Division of
Laboratory Sciences (DLS).

NHANES III DNA Specimens

The laboratory will distribute aliquots (samples) of crude DNA lysates extracted from cell lines. DNA concentrations vary and are estimated to range from 7.5-65.0 ng/ μ L with an average of approximately four micrograms in 100 μ L. Samples will be provided in 96 well plates that are bar-coded and labeled with a readable identifier. Quality control samples (5% of the total) will be sent at no charge, on separate plates as blind replicates. DNA specimens are available from 7,159 NHANES III participants. Samples will be distributed in a total of 78 plates with an additional four plates of quality control samples. NHANES III DNA specimens are in limited supply thus are not available as a partial set. Due to the method of extraction, NHANES III DNA specimens are not appropriate for all projects and/or assays.

NHANES 1999-2002, 2007-08, 2009-10 DNA Specimens

The laboratory will distribute aliquots of purified, high molecular DNA in normalized concentrations of 50.0

ng/ μ L. Some specimens may fall below this threshold. A sample of 40 microliters of each specimen will be supplied. The amount of DNA in each sample may vary but will be on average approximately two micrograms.

There are purified DNA specimens from 7,839 NHANES 1999–2002 participants. Samples from these specimens will be distributed into 90 plates including four plates of quality control samples.

There are purified DNA specimens available from 4,612 NHANES 2007–08 participants. These will be distributed into approximately 54 plates including three plates of quality control samples.

There are purified DNA specimens available from 4,893 NHANES 2009–10 participants. Samples from the specimens will be distributed into 54 plates with approximately three additional plates of quality control samples.

Each 96 well plate will be bar-coded and labeled with a readable identifier. Quality control samples (5% of a collection) will be sent at no charge, on separate plates as blind replicates.

Proposed Cost Schedule for Providing NHANES DNA Samples

Costs are determined by NCHS and include costs incurred from the contracting DNA Repository and DHANES administrative costs. The fee covers the costs of materials, equipment, labor, proposal review, administration and space for storage. For more details see Table 1 below. In prior years, the DNA Repository was maintained by CDC. The DNA Repository is now maintained by a private contractor. The costs of contracting, along with annual inflation increases, are reflected in the proposed cost schedule.

Procedures for Proposals

The investigator should follow these instructions for preparation of proposals. Protocols must be written using the outline below.

Proposal timeline:

- *Submission of Proposals:* Can be submitted on an ongoing basis
- *Scientific Review:* Within two months of proposal submission
- *Institutional Review Date:* Within six weeks of final proposal acceptance

- *Notification of approval:* Approximately 30 days after Institutional Review.
- *Anticipated distribution of samples:* Approximately 60 days after all approvals are obtained.

Note: Timeframe may vary depending on the nature of the proposal and the results of each level of review.

Unforeseen circumstances could result in a change to this schedule.

DNA Specimen Program will begin accepting research proposals on [INSERT DATE 60 DAYS AFTER PUBLICATION IN THE FEDERAL REGISTER].

In addition to the cover page, the research proposal should contain the title of the research project, the name, address phone number and E-mail address of the lead investigator along with the name of the institution where the testing will be conducted. Office of Human Research Protections assurance numbers for the institutions engaged in the research project should be included. CDC investigators need to include their Scientific Ethics Verification Number. E-mail submission of the proposal is required.

The proposals should be a maximum of 20 single-spaced typed pages, excluding figures and tables. Please use

appendices sparingly. If a proposal is approved, the title, specific aims, name, and phone number of the author will be maintained by NCHS and released if requested by the public. Unapproved proposals will be returned to the investigator and will not be maintained by NCHS.

Applications will have a Scientific Review by the Genetic Project Officer and the Technical Panel. The Technical Panel is comprised of two members: a Genetic Research Scientist and a Genetic Epidemiologist. The members review each proposal for scientific and technical merit.

After the proposal is approved by the Genetic Technical Panel and the Genetic Project Officer it will be submitted for Institutional review. All proposals will undergo Institutional Review by the NCHS Human Subjects Contact and the NCHS Ethics Review Board (ERB) for any potential human subjects concerns to ensure appropriate human subjects protections are provided in compliance with 45 CFR 46, and by the NCHS Confidentiality Officer for disclosure risk. The ERB will review the proposal even if the investigator has received approval by their institutional review panel.

Proposals should include the following information:

(1) *Cover sheet:* Include the name of the institution where the test will be conducted and Office of Human Research Protections assurance numbers for the institutions engaged in the research project. CDC investigators need to include their Scientific Ethics Verification Number.

(2) *Abstract:* Please limit the abstract to 300 words.

(3) *Specific Aims:* List the broad objectives; describe concisely and realistically what the research is intended to accomplish, and state the specific hypotheses to be tested.

(4) *Background and Public Health Significance:*

(A) Describe the public health significance of the proposed research.

(B) Discuss how the results will be used. Analyses should be consistent with the NHANES mission to assess the health of the nation. The Scientific Review will ensure that the proposed project does not go beyond either the general purpose for collecting the blood samples for DNA in the survey or the specific stated goals of the proposal.

(5) *Design, Method, and Data analysis:* The appropriateness and adequacy of the methodology proposed to reach the research aims, and the appropriateness of using the NHANES (a complex, multistage probability sample of the

national population) to address the goals of the proposal will be assessed.

(A) *Research Design and Methods*: Describe the analytic and statistical methods to be employed. Include power calculations. For all proposal categories, include a detailed description of the laboratory methods. The characteristics of the laboratory assay, such as reliability, validity, should be included with appropriate references. The potential difficulties and limitations of the proposed procedures should also be discussed. Address adequate methods planned for handling and storage of samples of DNA specimens. Proposals *must* specify specific variants or the standard assay(s) that will be used to test the proposed research hypotheses and include a statement of why the specific standard assay(s) is/are necessary to test the proposed hypotheses. The standard assay is a commercially available assay for a curated set of variants.

(1) Proposals will be provided with quality control samples at no additional cost. Approved projects must run these quality control samples and submit these results along with the results from the NHANES DNA samples, unless the Genetic Project Officer has approved an alternative quality control review plan. (2) Proposals using residual samples should have residual quality control samples and investigators

will be required to use these residual quality control samples. The proposal should address additional quality control procedures the laboratory will use to assure the validity of the test results and address adequate methods planned for handling and storage of sample specimens.

B) *Data analysis: Note: All resulting data must be analyzed in the NCHS RDC Output:* Please describe the data output that you would like to retain and take out of the RDC after analyses.

(6) *Additional information for NHANES:*

(A) *Clinical Relevance of Research Findings:* The consent document for DNA specimen storage and future studies states that individual results will not be provided to participants therefore no tests that would need to be reported back to the participant can be proposed.

NHANES/NCHS will use the most recent American College of Medical Genetics and Genomics (ACMG) recommendations for reporting incidental findings to review the proposed tests and the potential incidental findings. Investigators must justify that the proposed tests do not produce sets of variants on specific genes listed by the most recent ACMG as reportable incidental findings as well as how potential incidental test results will be handled. As of publication the most recent report, published July 2013, "ACMG

Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing”, lists 56 genes where specific variants on these genes are pathogenic for 24 conditions.

(B) *Data Transfer*: Specify the secure method to transfer resultant data to NCHS. Investigators must use a device that meets federal information processing standards (FIPS 140-2 and FIPS 197).

(C) *Period of Performance*: Specify the project period. The period may be up to three years. At the end of the project period, any unused samples must be returned to the NHANES DNA Specimen Repository or destroyed by the investigator. Extensions to the period of performance may be requested.

(D) *Funding*: Include the source and status of the funding to perform the requested laboratory analysis. Investigators will be responsible for the cost of processing and shipping the samples (*See table*).

(7) *References*

(8) *Resumes/CV*: Please include a 2-page CV for each member of the research team in this document (not as attachments).

Public Availability of Data

Data resulting from use of DNA specimens will be made available to the public for secondary data analyses via the NCHS RDC. After DHANES/NCHS quality control assessment is completed, investigators will be given up to six months to conduct comprehensive quality assurance review in the NCHS RDC. The quality assurance review timeframe will be negotiated between the investigator and the NHANES Genetic Project Officer and will depend on the type, number, and characteristics of the tests submitted. The results of the quality assurance review will be provided to DHANES/NCHS and appropriate aspects will become part of the data set documentation. The public announcement, that test results are available for submission of proposals for secondary data analyses, will occur once the quality assurance review timeframe has ended. For a list of currently available variant data see:

<http://www.cdc.gov/nchs/nhanes/biospecimens/dnaspecimens.htm#Genetic>.

Proposals for secondary data analyses linking NCHS restricted data, NCHS public use data, or non-NCHS data to data resulting from DNA specimen testing will be reviewed by the NCHS RDC. See <http://www.cdc.gov/rdc> for proposal guidelines.

Submission of Proposals

Proposals can be submitted immediately. The review process will begin approximately 60 days from the publication of the notice and will include all proposals submitted as of that date.

Electronic submission of proposals are required. Please submit proposals to the NHANES Genetic Project Officer : Jody McLean M.P.H., Division of Health and Nutrition Examination Surveys, National Center for Health Statistics, Centers for Disease Control and Prevention, 3311 Toledo Road, Hyattsville, MD 20782, Phone: 301-458-4683, E-Mail: *NHANESgenetics@cdc.gov*.

Agency Agreement

Investigators must secure funding and sign terms and conditions agreements for the use of the DNA specimens with CDC/NCHS prior to the release of the NHANES DNA samples. Investigators must agree to use the specimens only for the approved tests and use the test results only for purposes as stated in the approved proposal, not link the results of the proposed research to any other data, and not use the DNA specimens for commercial purposes via a legally binding

Materials Transfer Agreement for non-government researchers or Interagency Agreement for government researchers. In addition, all investigators will be required to sign a Designated Agent Agreement (DAA) with CDC/NCHS in accordance with NCHS' confidentiality legislation, the Confidential Information Protection and Statistical Efficiency Act (CIPSEA; Title V of the E-Government Act of 2002 (Public Law 107-347)). The DAA is the mechanism by which CDC/NCHS may authorize designation of agents to exclusively perform activities needed to produce approved data on CIPSEA protected NHANES DNA specimens.

Approved Proposals

After DNA samples are received and testing is complete, the resulting data will be sent back to DHANES/NCHS for quality control (QC) assessment. While DHANES/NCHS QC assessment is under way the investigator can submit a NCHS RDC proposal to conduct comprehensive quality assurance review. Once the investigator's quality assurance review is complete and the results returned to DHANES/NCHS, the test results will be made available to the public and the investigator can submit an NCHS RDC proposal to request

linkage to NCHS restricted data, NCHS public use data, or Non-NCHS data to conduct their analysis.

After the comprehensive quality assessment process has been completed by the investigator, a list of variants generated from NHANES specimen testing will be made available to the public for potential solicitation via NCHS RDC proposals. The list of variants will be available in the NHANES Genetic Variant Search (<http://www.nhgeneticvariant.com/>). In addition, DHANES/NCHS quality control assessment procedures will be posted on the NHANES Genetic Repository website and/or available via email.

Progress Reports

A progress report will be submitted in the annual CDC/NCHS/ERB continuation report. An ERB continuation form will be sent to the investigator each year for project update. If an approved proposal is unable to obtain funding the proposal will be closed.

Termination of ERB Protocol

At the end of laboratory testing the ERB Protocol will be closed.

Disposition of Results and Samples

The provided DNA samples **cannot** be used for any purpose other than the specifically requested purpose outlined in the proposal and approved through the Scientific and Institutional Review. No DNA samples can be shared with others, including other investigators, unless specified in the proposal and so approved. Samples must be returned upon completion of the approved project or destroyed only with the written approval of the NHANES Genetic Project Officer. Test results from all studies using NHANES DNA specimens will be made available to the public for secondary data analyses. After the DHANES/NCHS quality control assessment is completed, investigators will be given up to six months to conduct a more comprehensive quality assurance review. The final quality assurance review timeframe will be negotiated between the researcher and the NHANES Genetic Project Officer and characteristics of the tests submitted. Proposals for secondary data analyses will be reviewed by the NCHS RDC on a rolling basis; see: <http://www.cdc.gov/rdc> for proposal guidelines.

All data analyses will be conducted via access modes available at NCHS RDC.

Dated: October 4, 2016

Sandra Cashman

Executive Secretary

Centers for Disease Control and Prevention

Table 1. Cost Schedule for NHANES DNA Specimens

Total costs	1999-2002, 2007-08, 2009-10 Complete set	1999- 2002, 2007-08, 2009-10 Partial set	NHANES III Complete set
Materials and Equipment - contractor: plates, reagents, assays, aliquoting and packaging samples; use of equipment	\$1.51	\$4.53	\$0.75
Labor - contractor: processing, handling, and shipping; NCHS: data quality control	\$4.98	\$24.90	\$2.49

Total costs	1999-2002, 2007-08, 2009-10 Complete set	1999- 2002, 2007-08, 2009-10 Partial set	NHANES III Complete set
Proposal review and Administrative expenses - contractor: inventory management and reporting; NCHS: management of proposal process non-NCHS: technical panel fees	\$3.02	\$6.04	\$1.51
Space - contractor: freezer use and maintenance	\$5.59	\$5.59	\$2.79
Cost per sample	\$15.10	\$41.06	\$7.55
Cost per new proposal 1999-2002 2007-2008 2009-2010 III	\$119,260 \$72,661 \$73,884	NA	\$54,050
Cost per additional proposal* 1999-2002 2007-2008 2009-2010 III	\$5,963 \$3,633 \$3,694	**	\$2,702

* Additional research using DNA specimens already obtained from previous solicitations.

** This charge will be 5 percent of the original cost.

Note: Applicable CDC overhead and NCHS management and oversight charges will be added to these rates for proposals coming from Federal agencies.

[FR Doc. 2016-24349 Filed: 10/6/2016 8:45 am; Publication Date: 10/7/2016]